4

PCT WORLD INTELLECTUAL PROPERTY ORGANIZATION
International Bureau

INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification 6 : A61K 45/06	A1	(11) International Publication Number: **WO 99/21585**
		(43) International Publication Date: 6 May 1999 (06.05.99)

(21) International Application Number: PCT/IB98/01789

(22) International Filing Date: 19 October 1998 (19.10.98)

(30) Priority Data:
97/13426 27 October 1997 (27.10.97) FR

(71) Applicant: LABORATOIRES UPSA [FR/FR]; 128, rue Danton, Boîte postale 325, F–92506 Rueil–Malmaison Cedex (FR).

(72) Inventors: CAMBORDE, François; 19, avenue du 18 Juin 1940, F–92500 Rueil–Malmaison (FR). CLOAREC, Alix; 26, rue des Biaunes, F–78510 Triel–sur–Seine (FR). NICOLAI, Eric; 2, rue Marie–Levasseur, F–92500 Rueil–Malmaison (FR). TEULON, Jean–Marie; 13, avenue Gilbert, F–78170 La Celle–Saint–Cloud (FR).

(74) Agent: MAYS, Julie; Bristol–Myers Limited Company, Patent Dept., Swakeleys House, Milton Road, Ickenham, Uxbridge UB10 8NS (GB).

(81) Designated States: AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GE, GH, GM, HU, ID, IL, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, UZ, VN, YU, ZW, ARIPO patent (GH, GM, KE, LS, MW, SD, SZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG).

Published
With international search report.
Before the expiration of the time limit for amending the claims and to be republished in the event of the receipt of amendments.

(54) Title: PHARMACEUTICAL COMBINATION OF A CYCLOOXIGENASE–2 INHIBITOR AND ACETAMINOPHEN OR AN OPIATE

(57) Abstract

The object of the present invention is a pharmaceutical composition, characterized in that it comprises as active principle, a combination of a cyclooxygenase–2 inhibitor and a compound selected from acetaminophen and the opiates.

FOR THE PURPOSES OF INFORMATION ONLY

Codes used to identify States party to the PCT on the front pages of pamphlets publishing international applications under the PCT.

AL	Albania	**ES**	Spain	**LS**	Lesotho	**SI**	Slovenia
AM	Armenia	**FI**	Finland	**LT**	Lithuania	**SK**	Slovakia
AT	Austria	**FR**	France	**LU**	Luxembourg	**SN**	Senegal
AU	Australia	**GA**	Gabon	**LV**	Latvia	**SZ**	Swaziland
AZ	Azerbaijan	**GB**	United Kingdom	**MC**	Monaco	**TD**	Chad
BA	Bosnia and Herzegovina	**GE**	Georgia	**MD**	Republic of Moldova	**TG**	Togo
BB	Barbados	**GH**	Ghana	**MG**	Madagascar	**TJ**	Tajikistan
BE	Belgium	**GN**	Guinea	**MK**	The former Yugoslav Republic of Macedonia	**TM**	Turkmenistan
BF	Burkina Faso	**GR**	Greece			**TR**	Turkey
BG	Bulgaria	**HU**	Hungary	**ML**	Mali	**TT**	Trinidad and Tobago
BJ	Benin	**IE**	Ireland	**MN**	Mongolia	**UA**	Ukraine
BR	Brazil	**IL**	Israel	**MR**	Mauritania	**UG**	Uganda
BY	Belarus	**IS**	Iceland	**MW**	Malawi	**US**	United States of America
CA	Canada	**IT**	Italy	**MX**	Mexico	**UZ**	Uzbekistan
CF	Central African Republic	**JP**	Japan	**NE**	Niger	**VN**	Viet Nam
CG	Congo	**KE**	Kenya	**NL**	Netherlands	**YU**	Yugoslavia
CH	Switzerland	**KG**	Kyrgyzstan	**NO**	Norway	**ZW**	Zimbabwe
CI	Côte d'Ivoire	**KP**	Democratic People's Republic of Korea	**NZ**	New Zealand		
CM	Cameroon			**PL**	Poland		
CN	China	**KR**	Republic of Korea	**PT**	Portugal		
CU	Cuba	**KZ**	Kazakstan	**RO**	Romania		
CZ	Czech Republic	**LC**	Saint Lucia	**RU**	Russian Federation		
DE	Germany	**LI**	Liechtenstein	**SD**	Sudan		
DK	Denmark	**LK**	Sri Lanka	**SE**	Sweden		
EE	Estonia	**LR**	Liberia	**SG**	Singapore		

PHARMACEUTICAL COMBINATION OF A CYCLOOXIGENASE-2 INHIBITOR AND ACETAMINOPHEN OR AN OPIATE

The object of the present invention is a novel pharmaceutical combination having application notably in the treatment of pain and inflammatory phenomena.

More specifically, the invention relates to a pharmaceutical composition which comprises, as active principle, a combination of a cyclooxygenase-2 inhibitor and a compound selected from acetaminophen and the opiates.

Selective cyclooxygenase-2 (COX-2) inhibitors constitute a novel class of non-steroid analgesic and anti-inflammatory agents. Such compounds have been described for example in the documents WO 94/15932, WO 96/03388 by GD Searle, WO 95/00501 by Merck & Frosst Canada Inc., WO 95/18799, WO 96/08482 by Merck & Co., and FR 2747123, FR 2747124 by the Applicant.

Amongst the particularly preferred compounds which have been described in the state of the art,

- 5-bromo-2-[4-fluorophenyl]-3[4-methanesulphonylphenyllthiophen, known under the code name of DuP 697 ;

- 4-[5-(4-methylphenyl)-3-(trifluoromethyl)pyrazol-1-yl]benzenesulphonamide known under the designation Celecoxib ;

- (Z)-3-[1-(4-chlorophenyl)-1-(4-methanesulphonylphenyl)methylene]-dihydrofuran-2-one known under the code name UP 454-21,

may be notably cited.

Generally, these compounds also possess anti-inflammatory and analgesic activities, the latter being demonstrated in various experimental inflammatory pain models.

However, it is known that the selective cyclooxygenase-2 inhibitors are inactive or not very active in the non-inflammatory acute pain tests. Thus, *Gans et al.*, J. Pharm. Exp. Ther. 1990 ; (254) : 180-187 have demonstrated that the product DuP 697 mentioned above is inactive in the phenylbenzoquinone test in the mouse.

Acetaminophen, or paracetamol, N-(4-hydroxyphenyl)acetamide, or 4'-hydroxyacetanilide, is a well-tolerated medicament which possesses an analgesic and

anti-pyretic activity and is commonly used in the symptomatic treatment of painful and febrile ailments at daily doses in the order of 500 to 3000 mg.

The opiate or morpholinic compounds are powerful centrally-acting analgesics indicated in the treatment of moderate to severe pain and are able to induce dependence and addiction in certain circumstances.

It has been discovered, and this constitutes the basis of the present invention, that the combination of a cyclooxygenase-2 inhibitor and a compound selected from paracetamol and the opiates possesses a significant analgesic effect at doses at which each one of the products constituting this combination is inactive or not very active. The beneficial effect of the combination in accordance with the present invention has been demonstrated both in inflammatory pain models and in acute pain models, and particularly in the phenylbenzoquinone (PBQ) test and the heated plate test in the mouse. The results obtained have shown that this combination possesses an analgesic activity greater than that of each one of these constituent products used alone at the same dose.

The potentiation effect thus demonstrated makes the use of low doses of each one of the constituent products of the combination possible by thus limiting their possible side effects.

Moreover, this combination enables treating pain of very varied origin in a larger number of patients.

Advantageously, the pharmaceutical combination in accordance with the present invention will be in a form suitable for an administration:

- via the oral route, such as simple or coated tablets, capsules or granules, for example;
- via the rectal route, such as suppositories for example
-via the parenteral route, such as injectable preparations for example
-via the ocular route, such as eye lotions or ophthalmic solutions for example;
-via the transdermal route

-via the nasal route, such as aerosols and sprays for example; or

-via the auricular route, such as drops for example.

Such a composition can be prepared, according to the methods known per *se*, by incorporating the active principle, consisting of the above-mentioned combination, with excipients usually used such as talc, gum arabic, lactose, starch, magnesium stearate, polyvidone, cellulose derivatives, cocoa butter, semi-synthetic glycerides, aqueous or non-aqueous vehicles, fats of animal or vegetable origin, glycols, wetting agents, dispersing agents or emulsifiers, silicone gels, certain polymers or co-polymers, preservatives, aromas and coloring agents.

In general, any compound having a cyclooxygenase-2 inhibiting activity can be used within the context of the present invention, preferably, diaryl methylidenetetrahydrofuran derivatives will be used such as those described in the applications FR 2747123 and FR 2747124 of the Applicant which are incorporated herein by reference.

A particularly preferred compound is (Z)-3-[1-(4-chlorophenyl)-1-(4-methanesulphonylphenyl)methylene]dihydrofuran-2-one known under the code name of UP 454-21.

The opiates which can be used within the context of the present invention may be of a different nature : powerful opiates, the top one of which is morphine, which can treat severe pain, such as morphine itself or oxycodone, or weak opiates, which can treat pain of moderate intensity, such as codeine or dextropropoxyphen.

Derivatives having a powerful central analgesic effect, oxycodone in particular, will be more particularly preferred, but also weak morphine agonists such as codeine and dextropropoxyphen in particular are preferred as well.

Advantageously, the pharmaceutical compositions according to the invention will be in the form of a unit dose.

In the pharmaceutical combination in accordance with the present invention, the weight ratio of the cyclooxygenase-2 inhibiting compound to the compound selected from acetaminophen and the opiates will be that which possesses the greater

synergy between the two combined compounds, it will be between 0.01 and 10 for the majority of the examples and will be preferably from 0.1 to 3.5.

The daily dose which can be used of the various compounds constituting the pharmaceutical combination in accordance with the present invention will of course depend upon the state of the patient to be treated.

A suitable daily dose of cyclooxygenase-2 inhibitor will generally be between about 50 mg and about 800 mg.

The pharmaceutical compositions in accordance with the present invention are suitable in the treatment of inflammatory phenomena as well as in the treatment of pain.

Their use may be cited for example in the treatment of arthritis, especially rheumatoid arthritis, spondylitis, gouty arthritis, osteoarthritis, juvenile arthritis, autoimmune diseases and lupus erythematosus.

These compositions can also be used within the context of the treatment of bronchial asthma, dysmenorrhea, tendinitis, bursitis, dermatological inflammations such as psoriasis, eczema, bums and dermatitis.

These compositions can also be used within the context of the treatment of gastrointestinal inflammations, Crohn's disease, gastritis and ulcerative colitis, in the prevention of cancer, especially adenocarcinoma of the colon, in the prevention of neurodegenerative diseases, particularly Alzheimer's disease, in the prevention of stroke and epilepsy, and in the prevention of premature labour.

Finally, these compositions can be used within the context of the treatment of pain symptoms, especially in the treatment of myalgia, articular pain or neuralgia, dental pain, herpes zoster and migraine, in the treatment of rheumatic complaints and pain of cancerous origin, and also as complementary treatments for infectious and febrile states.

The invention further covers a method of therapeutic treatment of mammals, characterized in that it consists in administering to this mammal a therapeutically

effective amount of a combination of a cyclooxygenase-2 inhibiting compound and a compound selected from acetaminophen and the opiates such as described previously.

This method especially enables treating inflammatory phenomena and pain.

Description of the Drawings

Figure 1 graphically illustrates the antinociceptive effect of oral *UP-454-21-codeine* combination in the phenylbenzoquinone writhing test in mice; Dunnett's test * and ** for $p<0.05$ and $p<0.01$ respectively, indicate a significant difference in comparison to the control group. Student's test + for $p<0.05$ indicates a significant difference between the combination and the UP-454-21 group. n = 6 per group.

Figure 2 graphically illustrates the antinociceptive effect of oral *UP-454-21-paracetamol* combination in the phenylbenzoquinone writhing test in mice; Dunnett's test *** indicates a significant difference in comparison to the control group for $p<0.001$. Student's test t^{ooo} indicates a significant difference in comparison to the UP-454-21 group for $p<0.001$. n = 6 per group.

Figure 3 graphically illustrates the antinociceptive effect of oral *UP-454-21-paracetamol* combination in the hot plate test (52 °C) in mice; Dunnett's test ** indicates a significant difference in comparison to the control group for $p<0.01$. Student's test t^{ooo} indicates a significant difference in comparison to the UP-454-21 group for $p<0.001$. n = 10 per group.

Figure 4 graphically illustrates the antinociceptive effect of oral *UP-454-21-dextropropoxyphene* combination in the hot plate test (52 °C) in mice; Dunnett's test *** indicates a significant difference in comparison to the control group for $p<0.001$. Student's test ^{ooo} indicates a significant difference between the combination and the UP-454-21 group for $p<0.001$. n = 10 per group.

Figure 5 graphically illustrates the antinociceptive effect of oral *UP-454-21-oxycodone* combination in the hot plate test (52 °C) in mice; Dunnett's test * for $p<0.05$ indicates a significant difference in comparison to the control group.

Student's test + for $p<0.05$ indicates a significant difference between the combination and the UP-454-21 group. n = 10 per group.

Figure 6 graphically illustrates the antinociceptive effect of oral *UP-454-21-paracetamol* combination on thermal nocieptive threshold after intraplantar injection of complete Freund's adjuvant in rats; Dunnett's test * for $p<0.05$ indicates a significant difference in comparison to the control group. n = 7 per group

Figure 7 graphically illustrates the antinociceptive effect of oral *UP-454-21 - oxycodone* combination in the kaolin-induced arthritis test in rat; Dunnett's test ** for $p<0.01$ indicates a significant difference in comparison to the control group. Student's test ++ for $p<0.01$ indicates a significant difference between the combination and the oxycodone group. n = 10 per group.

Figure 8 graphically illustrates the antinociceptive effect of oral *UP-454-21 - paracetamol* combination on carrageenin-induced hyperalgesia in rats; Dunnett's test ** indicates a significant difference in comparison to the control group. n = 10 per group.

Figure 9 graphically illustrates the antinociceptive effect of oral *UP-454-21 - oxycodone* combination on carrageenin-induced hyperalgesia in rats; Dunnett's test *, ** for $p<0.05$ and $p<0.01$ indicates a significant difference in comparison to the control group. n = 10 per group.

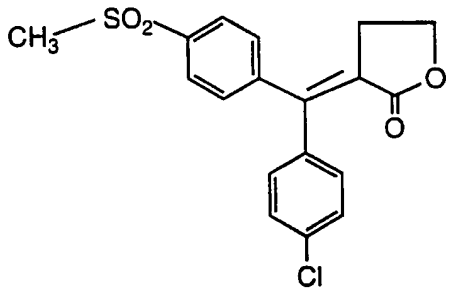
Figure 10 graphically illustrates the antinociceptive effect of oral *UP-454-21 - dextropropoxyphene* combination on carrageenin-induced hyperalgesia in rats; Student's test + indicates a significant difference between the combination and the UP-454-21 group for $p<0.05$. n = 10 per group.

Figure 11 graphically illustrates the antinociceptive effect of oral *UP-454-21 - codeine* combination on carrageenin-induced hyperalgesia in rats. Dunnett's test * for $p<0.05$ inidicates a significant difference in comparison to the control group. Student's test + for $p<0.05$ indicates a significant difference between the combination and the codeine group. n = 10 per group.

Demonstration of the analgesic properties of the pharmaceutical combination.

In order to demonstrate the specific analgesic properties of the pharmaceutical combination in accordance with the present invention, several pharmacological tests have been performed whose experimental protocols and results obtained will be given below.

In these tests, the compound used as an example of a selective cyclooxygenase-2 inhibitor is the compound known under the code name of UP 454-21 of the following general formula:



The results obtained for the first four tests are expressed in percentage inhibition of the pain reaction with respect to a control group.

Test no. 1 : phenylbenzoquinone test in the mouse

This test was carried out according to the method described by E. Siegmung,, R. Cadmus and G. Lu, A method for evaluating both non-narcotic and narcotic analgesics. Proc. Sec. Exp. Biol. Med. 1957 ; (95): 729-73 1.

One hour after the oral administration of the compound or the combination under study, a 0.02% solution of phenylbenzoquinone (PBQ) is administered via the intra-peritoneal route in the mouse.

The number of pain reactions (abdominal torsions and stretches) is then counted between the fifth and sixth minute after the injection of phenylbenzoquinone.

The results obtained are represented in Figures I and 2 which show the potentiation effect exerted by codeine (FIG. 1) and by paracetamol (FIG. 2) on the cyclooxygenase-2 inhibiting compound (UP 454-21).

Test no. 2 : Heated plate test

The test is carried out by following the experimental protocol described by N. B. Eddy, C.F. Toucheberry and J.E. Lieberman, Synthetic analgesics. 1 -Methadone isomers and derivatives. J. Pharmacol. Exp. Ther. 1950 ; (98) : 121137.

The mouse disposed on a plate heated to 52'C $\pm$ 0.05 shows its pain by licking its front paws, or more rarely by a jump.

The reaction time is then noted down, the maximum time being 30 seconds. The compounds or combinations studied are administered via the oral route one hour before the test.

The results obtained are represented in Figures 3 to 5 which clearly show the potentiation effect exerted by paracetamol (FIG. 3), by dextropropoxyphen (FIG. 4) and by oxycodone (FIG. 5) upon the cyclooxygenase-2 inhibitor (UP 454-21).

Test no. 3 : Plantar test

The test is carried out in the rat by following the experimental protocol described by R. Hargreaves, F. Brown, C. Flores and J. Joris, A new and sensitive method for measuring thermal nociception in cutaneous hyperalgesia. Pain. 1988 (32) : 77-88.

An inflammation is induced by intraplantar injection of a 0.05% suspension of Mycobacterium butyricum. Six hours after this injection, a heat stimulus (infrared ray) is applied onto the plantar face of the hind paw of the rat.

The nociceptive reaction of the animal manifests itself by the withdrawal or the licking of the paw.

The time of appearance of the pain reaction is then noted down.

The compounds and the combination studied are administered via the oral route one hour before the plantar test.

The results obtained are represented in Figure 6 which shows the effect of potentiation exerted by paracetamol upon the cyclooxygenase-2 inhibiting compound (UP 454-21).

Test no. 4 : Kaolin-induced arthritis test in the rat

An inflammation is induced by the administration of a 10% aqueous kaolin suspension into the tibio-femoral joint in the rat.

The compounds and the combinations studied are administered orally 30 minutes after the injection of kaolin.

The spontaneous painful behavior (discomfort in walking) is then quoted 5 and 6 hours after the injection of kaolin.

The results obtained are represented in Figure 7 which shows the effect of potentiation exerted by oxycodone upon the cyclooxygenase-2 inhibiting compound (UP 454-21).

Test no .5 : Paw pressure test in the carrageenin-induced hyperalgesia model

The inflammation is induced in the rat by plantar administration of a 2% carrageenin solution.

Three (3) hours after this injection, an increasing pressure is exerted upon the animal's paw.

The pain threshold, expressed in grams, is then noted down.

The compounds and the combinations studied are administered orally one hour before the paw pressure test.

The results obtained are represented in Figures 8 to 11 which show respectively the effect of potentiation exerted by paracetamol (FIG. 8), by oxycodone

(FIG. 9), by dextropropoxyphen (FIG. 10) and by codeine (FIG. 11) upon the cyclooxygenase-2 inhibiting compound (UP 454-21).

Several examples of pharmaceutical compositions according to the invention will now be given:

EXAMPLE I: UP 454-2 1/ACETAMINOPHEN COMBINATIONS

Example 1A: Capsule (size no. 0)

UP 454-21	50 mg
Acetaminophen	300 mg
Microcrystalline cellulose	80 mg
Hydroxypropyl methyl cellulose	10 mg
Magnesium stearate	20 mg

for a capsule

Example 1B: Tablet

UP 454-21	50 mg
Acetaminophen	300 mg
Microcrystalline cellulose	40 mg
Lactose	40 mg
Hydroxypropyl methyl cellulose	10 mg
Magnesium stearate	20 mg
Hydroxypropyl cellulose	50 mg

for a tablet

Example 1C: Suppository

UP 454-21	100 mg
Acetaminophen	600 mg
Semi-synthetic glyceride (suppocire)	1140 mg

for a suppository

Example 1D: Ophthalmic solution

UP 454-21	0.1%
Acetaminophen	1%
Castor oil (Cremophor EL)	5%
Polysorbate 80	5%
Water preparation for injection	q.s.p. 100%

Example 1E : Injectable preparation

UP 454-21	0.1%
Acetaminophen	1%
PEG 400	30%
Ethyl alcohol	20%
Water preparation for injection	q.s.p. 100%

EXAMPLE 2: UP 454-21/DEXTROPROPOXYPHEN COMBINATIONS

Example 2A: Capsule (size no. 1)

UP 454-21	50 mg
Dextropropoxyphen	20 mg
Microcrystalline cellulose	100 mg
Hydroxypropyl methyl cellulose	10 mg
Magnesium stearate	5 mg

for a capsule

Example 2B : Tablet

UP 454-21	50 mg
Dextropropoxyphen	20 mg
Microcrystalline cellulose	100 mg
Lactose	100 mg
Hydroxypropyl methyl cellulose	10 mg
Magnesium stearate	5 mg
Hydroxypropyl cellulose	50 mg

for a tablet

Example 2C : Suppository

UP 454-21 1 00 mg	
Dextropropoxyphen	40 mg
Semi-synthetic glyceride (suppocire)	1880 mg

for a suppository

Example 2D : Ophthalmic solution

UP 454-21	0.1%
Dextropropoxyphen	0.1%
Castor oil (Cremophor EL)	5%
Polysorbate 80	1%
Water preparation for injection	q.s.p. 100%

Example 2E : Injectable preparation

UP 454-21	0.1%
Dextropropoxyphen	0.1%
PEG 400	30%
Ethyl alcohol	10%
Water preparation for injection	q.s.p. 100%

EXAMPLE 3: UP 454-21/CODEINE COMBINATIONS

Example 3A: Capsule (size no. 1)

UP 454-21	50 mg
Codeine	20 mg
Microcrystalline cellulose	100 mg
Hydroxypropyl methyl cellulose	10 mg
Magnesium stearate	5 mg

for a capsule

Example 3B: Tablet

UP 454-21	50 mg
Codeine	20 mg
Microcrystalline cellulose	100 mg
Lactose	100 mg
Hydroxypropyl methyl cellulose	10 mg
Magnesium stearate	5 mg
Hydroxypropyl cellulose	50 mg

or a tablet

Example 3C : Suppository

UP 454-21	100 mg
Codeine	40 mg
Semi-synthetic glyceride (suppocire)	1880 mg

for a suppository

Example 3D : Ophthalmic solution

UP 454-21	0 - 1 %
Codeine	0.1%
Castor oil (Cremophor EL)	5.%
Polysorbate 80	1.%
Water preparation for injection	q.s.p 100 %

Example 3E : Injectable preparation

LT 454-21	0.1%
Codeine	0.1%
PEG 400	30.%
Ethyl alcohol	10%
Water preparation for injection	q.s.p. 100 %

EXAMPLE 4: UP 454-21/OXYCODONE COMBINATIONS

Example 4A : Capsule (size no. 1)

UP 454-21	50 mg
Oxycodone	15 mg
Microcrystalline cellulose	100 mg
Hydroxypropyl methyl cellulose	10 mg
Magnesium stearate	5 mg

for a capsule

Example 4B : Tablet

UP 454-21	50 mg
Oxycodone	15 mg
Microcrystalline cellulose	100 mg
Lactose	100 mg
Hydroxypropyl methyl cellulose	10 mg
Magnesium stearate	5 mg
Hydroxypropyl cellulose	50 mg

for a tablet

Example 4C : Suppository

UP 454-21	100 mg
Oxycodone	30 mg
Semi-synthetic glyceride (suppocire)	1900 mg

for a suppository

Example 4D : Ophthalmic solution

UP 454-21	0.1%
Oxycodone	0.06%
Castor oil (Cremophor EL)	5%
Polysorbate 80	1%
Water preparation for injection	q.s.p. 100%

Example 4E : Injectable preparation

UP 454-21	0.1%
Oxycodone	0.06%
PEG 400	30%
Ethyl alcohol	10%
Water preparation for injection	q.s.p. 100 %

What is claimed is:

1. A pharmaceutical composition, which comprises as active principle, a combination of a cyclooxygenase-2 inhibitor and a compound selected from the group consisting of acetaminophen and the opiates.

2. The pharmaceutical composition according to claim 1, characterised in that the cyclooxygenase-2 inhibiting compound is (Z)-3-[1-(4-chlorophenyl)-1-(4methanesulphonylphenyl)methylene]dihydrofuran-2-one.

3. The pharmaceutical composition according to claims 1 or 2, characterised in that said opiate compound is selected from the group consisting of oxycodone, codeine and dextropropoxyphen.

4. The pharmaceutical composition according to claims 1 to 3, characterised in that it is presented in a form suitable for an administration via a route selected from the group consisting of the oral route, the parenteral route, the rectal route, the ocular route, the transdermal route, the nasal route, and the auricular route.

5. The pharmaceutical composition according to claims 1 to 4, characterised in that the weight ratio of the cyclooxygenase-2 inhibiting compound to the compound selected from the group consisting of acetaminophen and the opiates is selected in order to lead to the greater synergy between the two combined compounds, the weight ration ranges preferentially from about 0.01 to 10, and more preferentially from 0.1 to 3.5.

6. The pharmaceutical composition according to claims 1 to 5, characterised in that it is presented as a unit dose containing from 50 mg to 200 mg of cyclooxygenase-2 inhibiting compound.

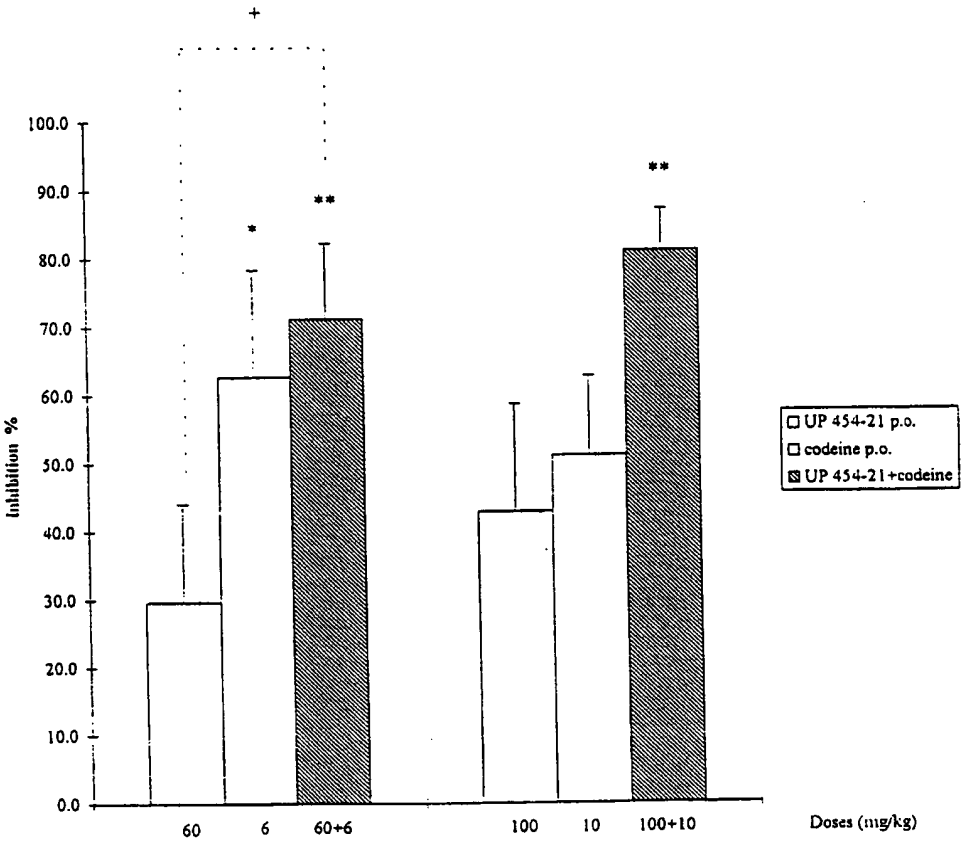

+
100.0
90.0
80.0
70.0
60.0
50.0
40.0
30.0
20.0
10.0
0.0
Inhibition %
*
**
**
UP 454-21 p.o.
codeine p.o.
UP 454-21+codeine
60
6
60+6
100
10
100+10
Doses (mg/kg)

Figure 1

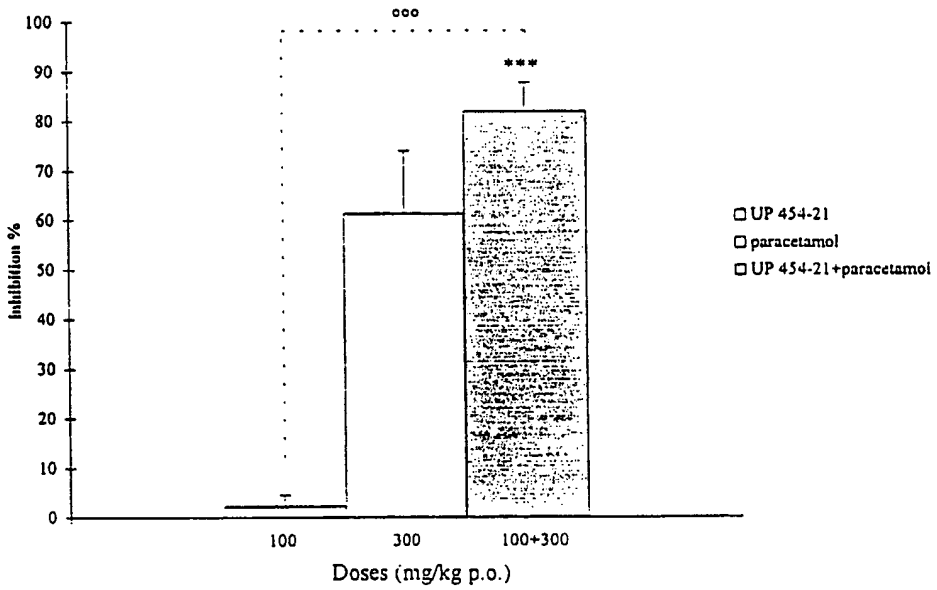

ooo
***
100
90
80
70
60
50
40
30
20
10
0
Inhibition %
100
300
100+300
Doses (mg/kg p.o.)
UP 454-21
paracetamol
UP 454-21+paracetamol

Figure 2

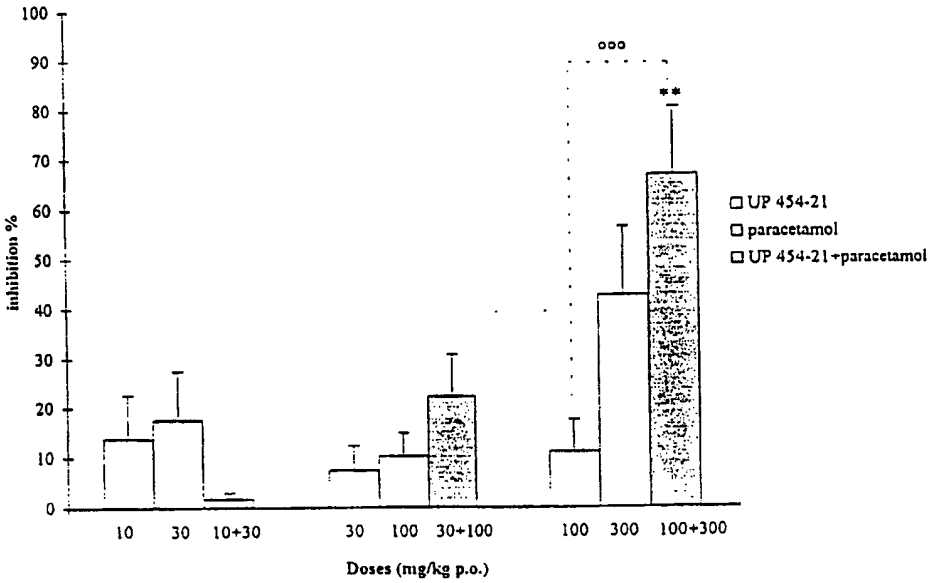

100
90
80
70
60
50
40
30
20
10
0
inhibition %
ooo
**
10
30
10+30
30
100
30+100
100
300
100+300
Doses (mg/kg p.o.)
UP 454-21
paracetamol
UP 454-21+paracetamol

Figure 3

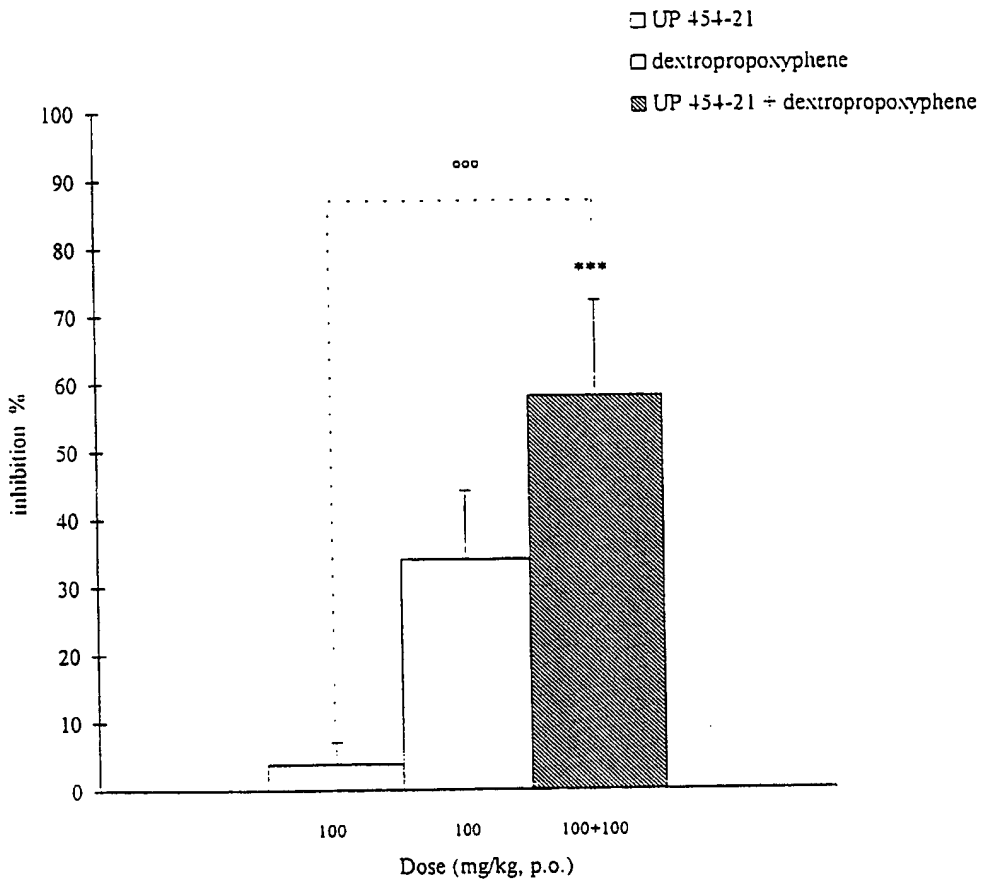

UP 454-21
dextropropoxyphene
UP 454-21 + dextropropoxyphene
inhibition %
100
90
80
70
60
50
40
30
20
10
0
ooo
***
100
100
100+100
Dose (mg/kg, p.o.)

Figure 4

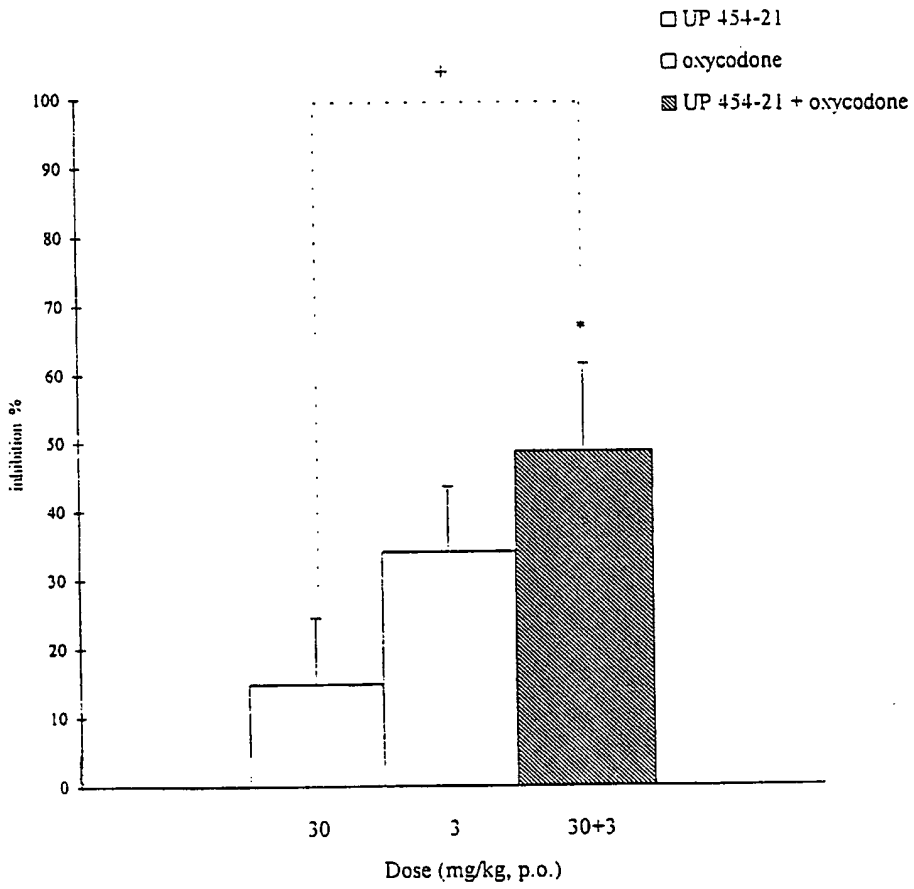

UP 454-21
oxycodone
UP 454-21 + oxycodone
100
90
80
70
60
50
40
30
20
10
0
inhibition %
30
3
30+3
Dose (mg/kg, p.o.)

Figure 5

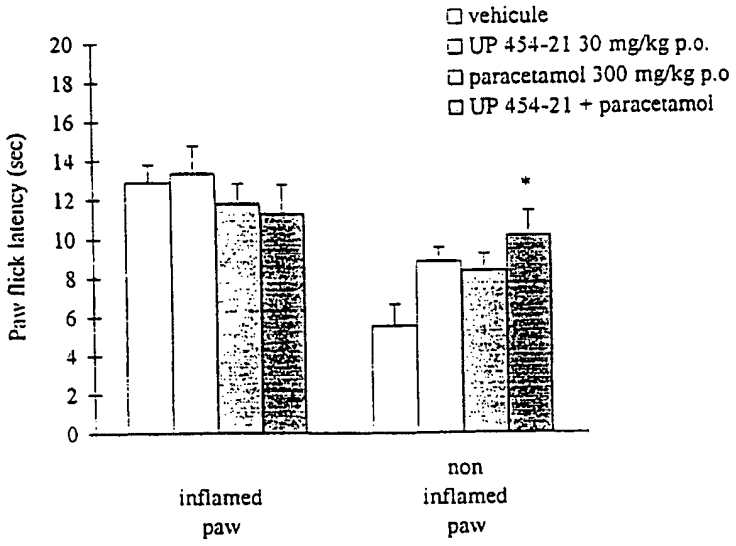

vehicule
UP 454-21 30 mg/kg p.o.
paracetamol 300 mg/kg p.o
UP 454-21 + paracetamol
Paw flick latency (sec)
20
18
16
14
12
10
8
6
4
2
0
*
inflamed paw
non inflamed paw

Figure 6

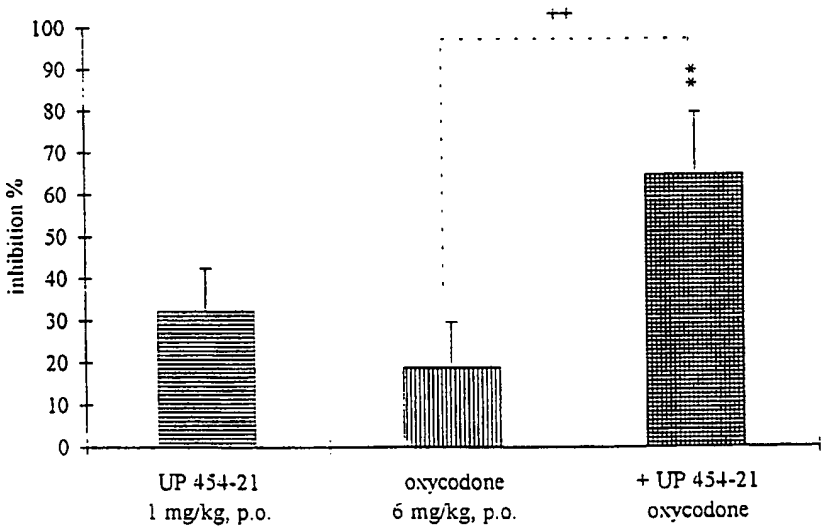

100
90
80
70
60
50
40
30
20
10
0
inhibition %
++
**
UP 454-21
1 mg/kg, p.o.
oxycodone
6 mg/kg, p.o.
+ UP 454-21
oxycodone

Figure 7

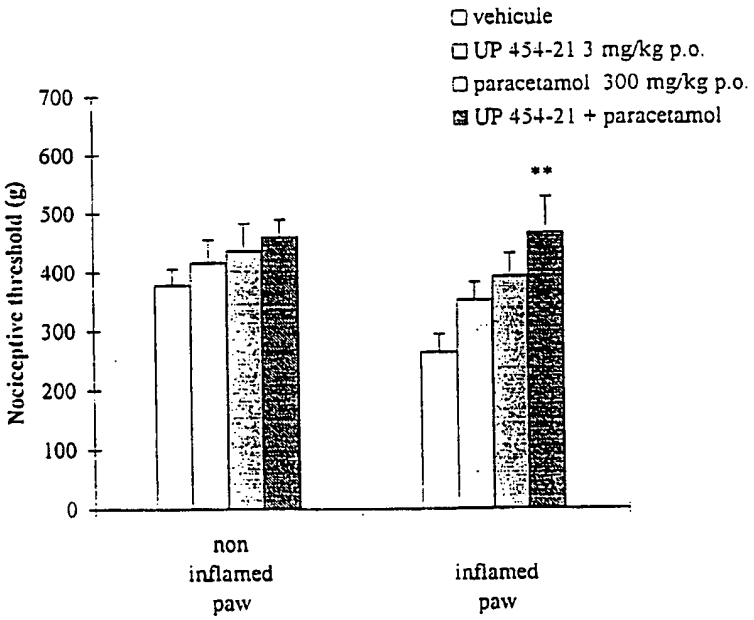

vehicule
UP 454-21 3 mg/kg p.o.
paracetamol 300 mg/kg p.o.
UP 454-21 + paracetamol
Nociceptive threshold (g)
700
600
500
400
300
200
100
0
**
non inflamed paw
inflamed paw

Figure 8

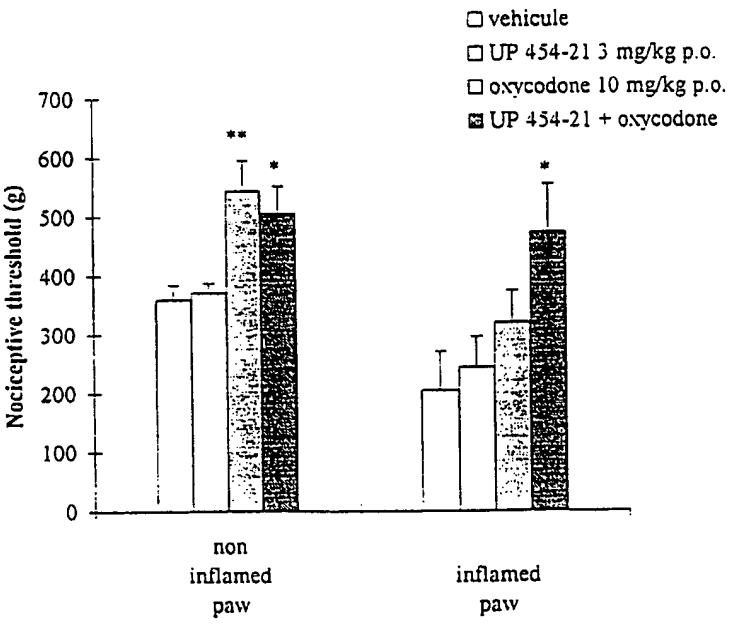

vehicule
UP 454-21 3 mg/kg p.o.
oxycodone 10 mg/kg p.o.
UP 454-21 + oxycodone
Nociceptive threshold (g)
700
600
500
400
300
200
100
0
**
*
*
non inflamed paw
inflamed paw

Figure 9

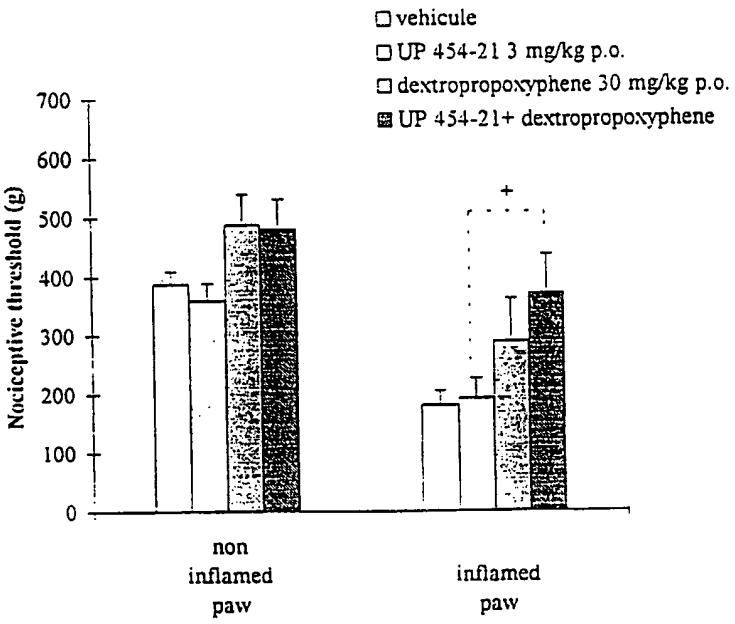

vehicule
UP 454-21 3 mg/kg p.o.
dextropropoxyphene 30 mg/kg p.o.
UP 454-21+ dextropropoxyphene
Nociceptive threshold (g)
700
600
500
400
300
200
100
0
+
non inflamed paw
inflamed paw

Figure 10

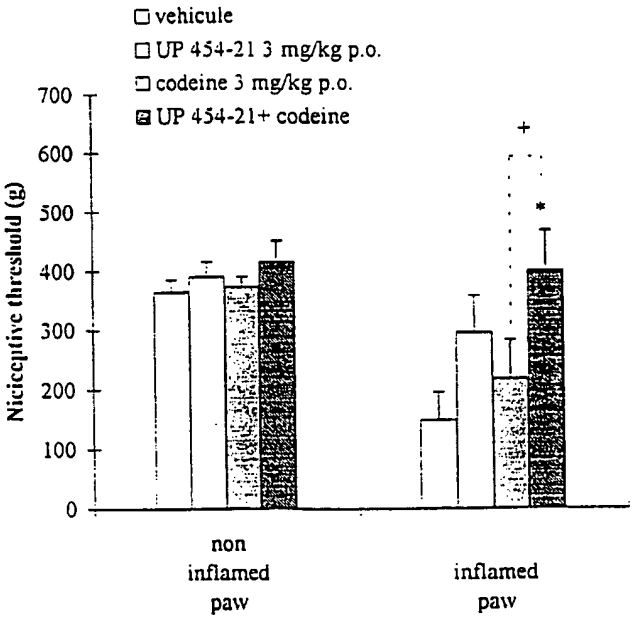

vehicule
UP 454-21 3 mg/kg p.o.
codeine 3 mg/kg p.o.
UP 454-21+ codeine
Nociceptive threshold (g)
700
600
500
400
300
200
100
0
+
*
non inflamed paw
inflamed paw

Figure 11

INTERNATIONAL SEARCH REPORT

International Application No
PCT/IB 98/01789

A. CLASSIFICATION OF SUBJECT MATTER
IPC 6 A61K45/06

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 6 A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 96 19469 A (MERCK FROSST CANADA INC ;BLACK CAMERON (CA); GRIMM ERICH (CA); LEG) 27 June 1996 see abstract see page 22, line 33 - page 23, line 18	1,3,4
X	WO 96 36623 A (MERCK FROSST CANADA INC ;BLACK CAMERON (CA); GRIMM ERICH (CA); WAN) 21 November 1996 see abstract see page 21, line 7 - line 26	1,3,4
X	US 5 552 422 A (GAUTHIER JACQUES Y ET AL) 3 September 1996 see column 9, line 25 - column 10, line 14	1,3,4

-/--

[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

° Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
25 March 1999	01/04/1999

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Leherte, C

Form PCT/ISA/210 (second sheet) (July 1992)

INTERNATIONAL SEARCH REPORT

International Application No
PCT/IB 98/01789

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication,where appropriate, of the relevant passages	Relevant to claim No.
X	US 5 521 213 A (PRASIT PETPIBOON ET AL) 28 May 1996 see column 5, line 56 - column 6, line 22 ---	1,3,4
X	WO 96 31509 A (GLAXO GROUP LTD ;BESWICK PAUL JOHN (GB); CAMPBELL IAN BAXTER (GB);) 10 October 1996 see page 5, line 13 - page 7, line 32 ---	1,3,4
X	WO 97 14691 A (MERCK FROSST CANADA INC ;BELLEY MICHEL (CA); GAUTHIER JACQUES Y (C) 24 April 1997 see page 42, line 11 - page 43, line 7 -----	1,3,4

1

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No
PCT/IB 98/01789

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 9619469 A	27-06-1996	AU 702591 B	25-02-1999
		AU 4294196 A	10-07-1996
		CA 2206978 A	27-06-1996
		EP 0799218 A	08-10-1997
		JP 10511089 T	27-10-1998
WO 9636623 A	21-11-1996	US 5691374 A	25-11-1997
		AU 5642496 A	29-11-1996
		CA 2219129 A	21-11-1996
		EP 0828724 A	18-03-1998
US 5552422 A	03-09-1996	AU 697650 B	15-10-1998
		AU 4381496 A	31-07-1996
		CA 2209895 A	18-07-1996
		WO 9621667 A	18-07-1996
		EP 0802917 A	29-10-1997
		JP 11501902 T	16-02-1999
US 5521213 A	28-05-1996	AU 689302 B	26-03-1998
		AU 3249295 A	22-03-1996
		CA 2197895 A	07-03-1996
		WO 9606840 A	07-03-1996
		EP 0778834 A	18-06-1997
		JP 10504829 T	12-05-1998
WO 9631509 A	10-10-1996	AU 5276696 A	23-10-1996
		BR 9604870 A	26-05-1998
		CA 2216809 A	10-10-1996
		CN 1186492 A	01-07-1998
		CZ 9703133 A	18-03-1998
		EP 0819127 A	21-01-1998
		HU 9801602 A	30-11-1998
		JP 11501049 T	26-01-1999
		NO 974595 A	03-12-1997
		NZ 304886 A	25-11-1998
		PL 322623 A	02-02-1998
		SK 133297 A	08-07-1998
WO 9714691 A	24-04-1997	AU 7123696 A	07-05-1997
		CA 2233178 A	24-04-1997
		CN 1200119 A	25-11-1998
		CZ 9801101 A	16-09-1998
		EP 0863891 A	16-09-1998
		HR 960458 A	30-04-1998
		JP 11500146 T	06-01-1999
		NO 981628 A	27-05-1998
		PL 326203 A	31-08-1998